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(54) Title: QUANTITATIVE AND QUALITATIVE IN VIVO TISSUE EXAMINATION USING TIME RESOLVED SPECTROSCOPY

(57) Abstract

A system for examination of biological tissue of a subject (10) includes a light source (14), (16), a light detector (22), a gated integrator (26), (28), and an integrator timing control (19) adapted to integrate detected photons over at least two selected time intervals. The light source (14), (16) is adapted to introduce into the tissue, at an input port, pulses of electromagnetic radiation of a selected wavelength in the visible or infrared range. The detector (22) detects photons of modified pulses that have migrated in the tissue from the input port. The integrator (26), (28) registers all photons detected over preselected time intervals of the arrival time of the modified pulses. A processor (30) adapted to receive data from the integrator (26), (28) determines a physiological property of the examined tissue based on the number of photons integrated over each time interval.

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QUANTITATIVE AND QUALITATIVE IN VIVO TISSUE EXAMINATION
USING TIME RESOLVED SPECTROSCOPY

Background of the Invention

5   The present invention relates to a time resolved
spectroscopy method and apparatus for *in vivo*
characterization of tissue.

        Continuous wave (CW) tissue oximeters have been
widely used to determine *in vivo* concentration of an
10   optically absorbing pigment (e.g., hemoglobin,
oxyhemoglobin) in biological tissue. The CW oximeters
measure attenuation of continuous light in the tissue and
evaluate the concentration based on the Beer Lambert
equation or modified Beer Lambert absorbance equation.
15   The Beer Lambert equation (1) describes the relationship
between the concentration of an absorbent constituent
(C), the extinction coefficient (ϵ), the photon migration
pathlength <L>, and the attenuated light intensity
(I/I_o).

$$\frac{\log [I/I_0]}{<L>} = \sum \epsilon_i C_i \qquad (1)$$

20   The CW spectrophotometric techniques cannot determine ϵ,
C, and <L> at the same time. If one could assume that
the photon pathlength were constant and uniform
throughout all subjects, direct quantification of the
constituent concentration (C) using CW oximeters would be
25   possible.

        In tissue, the optical migration pathlength varies
with the size, structure, and physiology of the internal
tissue examined by the CW oximeters. For example, in the
brain, the gray and white matter and the structures
30   thereof are different in various individuals. In
addition, the photon migration pathlength itself is a
function of the relative concentration of absorbing

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constituents. As a result, the pathlength through an
organ with high blood hemoglobin concentration, for
example, will be different from the same with a low blood
hemoglobin concentration. Furthermore, the pathlength is
5 frequently dependent upon the wavelength of the light
since the absorption coefficient of many tissue
constituents is wavelength dependent. Thus, where
possible, it is advantageous to measure directly the
pathlength when quantifying the hemoglobin concentration
10 in tissue.

Frequently, it is advantageous to determine the
hemoglobin saturation in vivo. Although the arterial
oxygen saturation in a perfused organ can be quantified,
it is not possible to estimate the change in the
15 hemoglobin oxygen concentration as it leaves an artery
and enters the capillary bed; nor is it possible to
determine the intermediate value of oxygen saturation in
a particular capillary bed from the venous drainage since
no technique has been devised for drawing a blood sample
20 directly from the capillary bed.

In contrast to CW oximeters, time resolved
spectroscopy (TRS-pulse) can measure directly the average
pathlength of migrating photons as well as other tissue
properties such as the absorption and scattering of light
25 in tissue.

As described in the above-cited patent and patent
applications, the TRS system irradiates tissue with
pulses of light of 10^{-10} sec. duration that migrate
through a path between an optical input port and an
30 optical detection port. The shape of the input pulse is
modified by the scattering and absorption properties of
the tissue. The modified light is detected by a photo-
multiplier, amplified and stored in a multichannel
analyzer. The multichannel analyzer collects only a
35 single photon for each input light pulse. A signal from

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each detected photon is encoded for time delay and
recorded. The pulses are accumulated over a relatively
long time interval (on the order of 5 minutes) so that
approximately 10^5 counts are collected at the detected
5 pulse maximum. The relatively long counting time is
required to obtain reasonable statistics so that a
reasonable fit over three or four decades of the
logarithmic slope on the detected pulse can be obtained.

For some applications, the relatively long
10 collection time is a disadvantage. Furthermore, the
instrumentation of the single photon counting TRS-pulse
system is costly when compared with the CW systems. The
relative complexity, cost, and size of the TRS-pulse
system, of the embodiment illustrated in U.S. Patent No.
15 5,119,815, could present some barriers to marketing for
certain applications in today's cost-conscious health
care industry.

Thus, there is a need for a cost-effective time
resolved spectroscopic system that requires a relatively
20 short period of data accumulation for quantitative and
qualitative tissue examination.

                    Summary of the Invention

In one aspect, the invention features a method and
a system for examination of biological tissue of a
25 subject using a light source, an optical detector, a
gated integrator with an integrator timing control and a
processor. The scattering and absorptive properties of
the examined tissue are determined by photons migrating
between an optical input port connected to the source and
30 an optical detection port connected to the detector. The
light source is adapted to introduce into the tissue, at
the input port, pulses of electromagnetic radiation of a
selected wavelength in the visible or infra-red range,
the pulses having duration on the order of a nanosecond
35 or less. The detector is adapted to detect, at the

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detection port, photons of modified pulses that have
migrated in the tissue from the input port. The gated
integrator and the integrator timing control are adapted
to integrate the photons over at least two selected time
5 intervals separately spaced over the arrival time of the
modified pulses. The processor is adapted to determine a
physiological property of the examined tissue based on
the number of photons integrated over each time interval.

Preferred embodiments of this aspect of the
10 invention may include one or more of the following
features.

The system further includes an additional gated
integrator and integrator timing control adapted to
integrate the photons over a selected time interval
15 spaced over the arrival time of the modified pulses.

The processor can determine the absorption
coefficient (μ_a) of the examined tissue based on the
number of photons integrated over at least two selected
time intervals separately spaced over the arrival time of
20 the modified pulses.

The absorption coefficient is determined from the
decay slope of the arrival time of the modified pulses.

The gated integrator, the integrator timing
control and the processor are adapted to determine the
25 delay time (t_{max}) between the introduced pulse and a time
at which the detected profile of the corresponding
modified pulse has a maximum value.

The processor is further adapted to determine the
effective scattering coefficient $(1-g) \cdot \mu_s$ of the examined
30 tissue using the formula:

$$(1-g) \, \mu_s = \frac{1}{\rho^2} \, (4\mu_a c^2 t_{max}^2 + 10 c t_{max}) - \mu_a$$

wherein ρ is a distance between the input and detection
ports and c is speed of light in the medium.

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The light source is further adapted to introduce into the tissue, at the input port, the pulses of electromagnetic radiation of a second selected wavelength in the visible or infra-red range, and the detector is
5 further adapted to detect, at the detection port, photons of modified pulses of the second wavelength that have migrated in the tissue from the input port. The gated integrator and the integrator timing control are further adapted to integrate the detected photons over at least
10 two selected time intervals separately spaced over the arrival time of the modified pulses. The processor is further adapted to determine a physiological property of the examined tissue based on the number of photons integrated over each time interval for each selected
15 wavelength.

The absorption coefficient (μ_a) of the examined tissue can be determined by the processor based on the number of photons integrated over at least two selected time intervals separately spaced over the arrival time of
20 the modified pulses.

The processor is further adapted to determine concentration of a tissue pigment based on the absorption coefficients at each selected wavelength.

The processor is further adapted to determine the
25 oxygen saturation Y based on the ratio of the absorption coefficients at two selected wavelengths.

The gated integrator and the integrator timing control are further adapted to integrate the detected photons over several selected time intervals separately
30 spaced over the entire arrival time of the modified pulses, and the processor is further adapted to determine intensity profile of the modified pulses over the entire arrival time.

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The processor is further adapted to determine a mean pathlength of the distribution of the photon migration pathlengths.

The determined pathlength is used to calibrate
5   data measured by a continuous wave oximeter.

The light source includes a laser driven by a pulse generator and a pulser. The wavelength of the source is in the range of 600nm to 1000nm.

Brief Description of the Drawing

10   Fig. 1 is a block diagram of a two gate integrator TRS-pulse system in accordance with one embodiment of the present invention.

Fig. 2 is a timing diagram of the system of Fig. 1.

15   Fig. 3 is a block diagram of a single integrator single wavelength TRS-pulse system in accordance with another embodiment of the present invention.

Fig. 4 is a block diagram of a multiple gate integrator TRS pulse system in accordance with another
20   embodiment of the present invention.

Fig. 5 and 5A show a typical time resolved spectrum and a timing diagram for the system of Fig. 4, respectively.

FIG. 5B shows a time resolved spectrum of photons
25   that migrated through tissue with regions of different absorption and scattering properties.

Fig. 6 is a block diagram of a TRS-pulse system utilizing an additional reference fiber adapted for time calibration.

30   Fig. 6A is a time resolved spectrum that includes a modified pulse and a reference pulse.

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Description of the Preferred Embodiment

As described in Disclosure Document No. 301,998,
entitled Simplified TRS filed with The Patent and
Trademark Office on February 12, 1992, Fig. 1 (BC148 of
5   the disclosure document) illustrates the appropriate
electronic components, consisting of a 0.5 nanosecond
pulse generator (12) operating at 100 MHz and a pulse
train at 100 MHz with a duration of 0.5 nanosecond.
These pulses are alternately switched to the 670 nm laser
10 diode (14) or to the 816 nm laser diode (16) to
illuminate the subject (10), for example, the forehead,
at a frequency of 50 MHz. The output (20) is detected by
an R928 PMT (22) connected to a wide band
amplifier/impedance changer (24) and then to the two
15 parallel pulse integrators (26 and 28). These pulse
integrators are activated at the times corresponding to
the illumination of the subject by the two wavelengths
(670 and 816 nm). The trigger generator for this follows
the timing diagram (Fig. 2) and consists of two trigger
20 generating circuits (15, 17), each triggered by a diode
pick up from the corresponding light source. Thus the
integrators (26 and 28) are activated only when the
particular light source is activated. Their outputs (27
and 29) are connected to the subtraction and ratio
25 circuit (30), so that the output is the ratio of the two
wavelengths, which, in turn, is connected to a simple
computer (32) for saturation.

The gate and delay generator (19) operates in
accordance with the timing diagram (Fig. 2) and consists
30 of two generators, each separately triggered by the
appropriate trigger pulse (alternatively, the same gate-
generating components can be time shared with electronic
switches).

A trigger pulse (36) obtained from the 670nm light
35 source sets off the timing diagram (34) to afford a delay

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gate (38) for gate pulse 1 (40), which is from 2-2.7
nanoseconds. The gate triggers a pulse integrating
circuit (26) which integrates detected photons (41). The
same is done for the 816nm light source wherein the gate
5   (19) triggers the second pulse integrating circuit (28).
Subsequently, the delay time of delay gate 2 is chosen so
that delay gate 2 (42) triggers gate pulse 2 (44) from
3.8-5.4 nanoseconds for pulses from the two light sources
as described above.

10   An analog voltage is then available which
represents this integral, which is then converted into
logarithms with an analog (or digital) circuit. The
result of these logarithms, divided by the known time
difference between the two, gives, with proper scaling,
15 μ_a for the particular wavelength - for example, 670 nm.
Another wavelength is available, namely 816 nm, so that
the μ_a values of the two wavelengths can be obtained and
entered into the usual calculation for saturation (32).

        Fig. 3 shows diagrammatically another
20 implementation of the "boxcar" simplified TRS system that
uses a single integrator for the gated photon signal
integration. A pulse generator 52 operating at a
frequency on the order of 100 MHz connected to a pulser
54 drives a laser 56 (e.g., Hamamatsu PLP-10 pulsed laser
25 diode). Laser 56 generates a train of light pulses of a
selected wavelength (e.g., 754 nm) and constant duration
on the order of 100 psec (Pulses of the order of a
nanosecond can also be used). The light pulses are
coupled to an optical fiber 58 and are introduced to
30 subject 50 at an input port. Transmitted photons migrate
in the subject and arrive at a detection port of an
optical fiber 60. In the migration process, the input
pulse has been modified by the scattering and absorptive
properties of tissue of subject 50. Photons arriving at
35 the detection port are transmitted to a detector 62, (for

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example, Hamamatsu photomultipliers R928, R1517, MCP
R1712, R1892 or other).

The output of detector 62 is amplified in a wide
band preamplifier/impedance changer 64 and coupled to a
5   boxcar integrator 66. Integrator 66 activated by a pulse
gate collects all arriving photons over a predetermined
time interval. The integrator output (72) is sent to
computer interface module 74. Computer 76 stores the
total number of counts detected during the collection
10 interval of integrator 66.

Integrator 66 includes a trigger 65 that is
triggered by a signal 55 from pulser 54. Trigger 65
activates a delay gate 67 that, in turn, starts counting
of all detected photons during the time interval
15 specified by a gate width circuit 69. Output from a gate
width normalizer 71 is an analog signal or a digital
signal representing all photons that arrived at the
detection port during the preselected gate width
interval. A suitable integrator can be achieved by using
20 SR 250 manufactured by Stanford Research Systems.

Depending on the application, computer 76 sets the
delay time of delay gate 67 and the gate width time of
gate width circuit 69. The system can scan integration
gate widths over the whole time profile of the detected
25 pulse. Gate width normalizer 71 adjusts the width of the
integration time depending on the detected signal level.
The gate width may be increased logarithmically for
smaller signals in accordance with the exponential decay
of the fall of the detected pulse; this increases the
30 signal to noise ratio. The system operates at a
repetition rate of at least 10KHz.

Referring to Fig. 4, alternatively, multiple (at
least three), parallel integrators are used in a faster
and more efficient system. This system, same as the
35 system of FIG. 3, may be used to determine the whole

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profile of the detected pulse (89) shown in Fig. 5, by
appropriately selecting the delay gates and the gate
widths.

5   Pulse generator 52 connected to a pulser 54 drive
alternately laser 56 and 57. The alternate coupling is
provided by a switcher 53 that operates at frequencies on
the order of 10^7Hz. Pulses of light of wavelength in the
visible or infra-red range and duration 10^{-9} to 10^{-10}
second are alternately coupled to subject 10 via optical
10   fibers 98 or other light guide. The light pulses are
modified by tissue of subject 50 positioned between the
input port of fiber 98 and the detection port of fiber
100. The modified pulses are detected by detector 102
and the detected signal is amplified by preamplifier 104.
15   Integrators 80, 82, and 84 collect data during selected
gate width intervals, as shown on the timing diagram of
Fig. 5A. Trigger 55 correlated with the input pulse,
triggers delay gates 1, 2, and 3 (shown in Fig. 5A) that
are set to have selected delay times. Each delay gate
20   then triggers its corresponding integrator that collects
all photons that arrive at the detector during the delay
width time. Each integrator collects photons arriving at
the detection port during its integration time defined by
the gate width. This configuration can achieve a
25   repetition rate of at least 10 kHz.

     The gate arrangement of FIGS. 5 and 5A uses gates
91 and 95 to detect the decay slope of the signal while
the third gate 99 may be used to determine the background
signal. Outputs 92 and 96 of integrators 80 and 82 are
30   used to calculate the slope.

     To obtain approximately equal signal-to-noise
ratios in the individual integrators, the length of the
time windows is tailored to an exponential decay of the
signal intensity with a logarithmic increase in the gate
35   width with delay time.

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Referring to Figs. 5 and 5A, by scanning the delay
gates (90, 94, and 98) and appropriately adjusting the
gate widths, the system collects data corresponding to
the entire detected pulse; subsequently, the shape (89)
5 of the detected pulse is then calculated, i.e., time
dependent light intensity profile I(t) is determined.
The detected pulse shape, I(t), possesses information
about the scattering and absorption properties of the
examined tissue, which are closely related to the
10 distribution of photon pathlengths in the tissue. The
optical field is a function of the input-output port
separation (ρ) as well as the optical properties of the
tissue (absorption coefficient, μ_a, scattering
coefficient, μ_s, and the mean cosine of anisotropic
15 scattering, g). The general diffusion equation is used
to describe the photon migration in tissue, as described
by E.M. Sevick, B. Chance, J. Leigh, S. Nioka, and M.
Maris in Analytical Biochemistry 195, 330 (1991) which is
incorporated by reference as if fully set forth herein.
20   The system utilizes a previously determined
solution for the fluence distribution in an infinite
media as a Green's function with near infinite boundary
conditions, wherein the diffusion equation is solved for
the intensity of detected light in the reflectance
25 geometry, R(ρ,t), or the transmittance geometry T(ρ,d,t).
In the reflectance arrangement in a semi-infinite media
with the separation of the input and output ports on the
order of centimeters the reflectance was determined as
follows:

$$\frac{d}{dt}\log_e R(\rho, t) = \frac{-5}{2t} - \mu_a c + \frac{\rho^2}{4Dct} \qquad (2)$$

30   For t → ∞ the absorption coefficient μ_a is
determined as follows:
wherein ρ is the separation between input and detection
ports and c is speed of light in the medium.

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$$\lim_{t \to \infty} \frac{d}{dt} \log_e R(\rho, t) = - \mu_a c \qquad (3)$$

In cases where the approximation of infinite time is not valid, Eq. 2 can be rewritten to obtain μ_a as follows:

$$\mu_a c = - \frac{d}{dt} \log_e R(\rho, t) + \frac{\rho^2}{4Dct} - \frac{5}{2t} \qquad (4)$$

The value for D can either be an average value for tissue
5 or a value specific to tissue type being measured such as head or breast.

The effective scattering coefficient (1-g) μ_s is determined as follows:

$$(1-g) \mu_s = \frac{1}{\rho^2} (4 \mu_a c^2 t_{max}^2 + 10 c t_{max}) - \mu_a \qquad (5)$$

wherein t_{max} is the delay time at which the detected
10 reflectance time profile $(R(\rho,t) \equiv I(t))$ reaches maximum. The right hand side of Eq. 3 is the decay slope of the arrival time of the modified pulses.

The systems of Figs. 1, 3, and 4 enable direct, real-time output of the absorption coefficient μ_a, tissue
15 saturation (Y), average optical pathlength (<L>), and the scattering coefficient μ_s. The absorption coefficient is quantified by evaluating the decaying slope of the detected pulse, as described in Eq. 3. The effective scattering coefficient, (1-g)·μ_s, is determined from Eq.
20 5.

As stated above, the intensity profile of the detected pulse, I(t), is strongly dependent on the absorption and scattering properties of the examined tissue. For a relatively homogeneous tissue (e.g.,
25 breast tissue), the detected pulse, in general, exhibits a single exponential decay (FIG. 5A). In cases wherein the light pulse migrates through different types of

tissues (e.g., brain tissue that includes the white matter and the gray matter), the detected profile (I(t)) includes "two or more superimposed pulses", each characteristic of one type of tissue (Note pulse shapes
5 105, 106, and 107 in FIG. 5B). The TRS system of FIGS. 1, 2 or 3 scans the delay gates over the entire arrival time delay of the migrating photons to collect and deconvolute the intensity profile, I(t). A computer processor then fits iteratively the intensity profile to
10 two or more overlapping curves and determines the scattering and absorption coefficients for each tissue effectively using Eqs. (3) and (5).

Photons introduced at the detection port are scattered on their migration path that depends on the
15 number of scattering events. In highly scattering tissue, the time-of-flight of photons is the longest and photons have the greatest probability of penetrating larger volumes of tissue. The time-of-flight (or mean time <t>) is proportional to the pathlengths travelled by
20 the photons, assuming that they travel at a speed c/n (wherein c is the speed of light in vacuum and n ≈ 1.36 is the average refractive index of tissue). From the detected and deconvoluted photon intensity profile, I(t), a mean pathlength of the distribution of pathlengths is
25 determined as follows:

$$<L> = \frac{c}{n} \frac{\int_0^\infty I(t)\, t\, \partial t}{\int_0^\infty I(t)\, \partial t} \qquad (6)$$

Photon migration theory predicts that the detected photons can be represented by a three dimensional "banana-shaped" distribution pattern in the reflection geometry or a "cigar-shaped" distribution pattern in the
30 transmission geometry. The concavity or shallow boundary is due to the escape of photons that reach the air-scatterer interface while the deeper boundary is due to

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attenuation of long path photons by the absorbers. If
the tissue absorption properties are nonuniform, for
example, when an absorbing object such as bleeding or a
tumor is present, then the distribution of pathlength is
5 also nonuniform.

The optical field is moved through tissue by
increasing ρ to achieve deeper field penetration or by
moving the input port and the detection port in a
scanning motion.

10   When the absorbing object is infinitely far away
from the field, it does not alter the banana-shaped
optical field. As the optical field is moved closer to
the strongly absorbing object, the photons which have
migrated the farthest distance from the input and
15 detection ports are eliminated by the absorption process
inside the absorber. Since photons with the longest
pathlengths are absorbed, the approach of the field to
the absorbing object shortens the distribution of
pathlengths, detected as reduction in the average
20 pathlength <L>. As the optical field moves even closer
to the absorbing object, some of the detected photons can
migrate around the object without being absorbed; this is
detected as lengthening of the distribution of
pathlengths. Thus, the average pathlength measurement
25 reveals location of a strongly absorbing component of a
tissue (e.g., tumor or localized bleeding); this is one
way how the tissue absorbing component can be imaged.

Alternately, localization of an absorbing (or
transparent) tissue component can be performed by moving
30 the input port and the detection port on the subject and
then creating two dimensional maps of absorption
coefficients, scattering coefficients, saturation values,
etc.

In the TRS system that includes two wavelengths
35 sensitive to hemoglobin (Hb) and oxyhemoglobin (HbO_2)

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(e.g., 754nm and 816nm), the hemoglobin saturation (Y) is
calculated by taking the ratio of absorption coefficients
and using the following equation for the oxygen
saturation:

$$Y(X100\%) = \frac{38 - 18 \frac{\mu_a^{754}}{\mu_a^{816}}}{25 + 3 \frac{\mu_a^{754}}{\mu_a^{816}}} \qquad (7)$$

5   wherein the coefficients are determined from the
extinction values of hemoglobin at 754 nm and 816 nm that
are $\varepsilon_{Hb} = 0.38 \ cm^{-1} \ mM^{-1}$, $\varepsilon_{Hb} = 0.18 \ cm^{-1} mM^{-1}$,
respectively, and the difference extinction coefficients
between oxyhemoglobin and hemoglobin that are $\Delta\varepsilon_{HbO-Hb} =$
10 0.025 $cm^{-1} \ mM^{-1}$ and $\Delta\varepsilon_{HbO-Hb} = 0.03 \ cm^{-1} \ mM^{-1}$, respectively.
        A single wavelength system of FIGS. 1, 3, and 4
can be employed for determination of the optical
pathlength of photons migrating in tissue for use with CW
oximeters. The pathlength is used in conjunction with
15 the attenuation data (I/I_0) from the oximeters to
quantitatively calculate the concentration of
oxyhemoglobin using Eq. 1.
        To account for difference between the geometric
distance (ρ) of the input port and the detection port and
20 the pathlength (<L>), some oximeters use a modified Beer-
Lambert equation with a differential pathlength factor
(DPF) as follows:

$$absorbance = DPF.\epsilon.[C] \qquad (7)$$

wherein [C] is the concentration of an absorbent
constituent. The differential pathlength factor can not
25 be precisely determined by the CW oximeters since it
depends on the pathlength, but it can be determined using
the absorption (μ_a) and scattering (μ_s) coefficients as
follows: Thus a TRS system can be used to calibrate a CW

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$$DPF = \frac{\sqrt{3}}{2} \sqrt{\frac{(1-g)\mu_s}{\mu_a}} \qquad (8)$$

oximeter to quantify the measured data.

In the studies of the brain, the TRS-pulse system
is used to obtain the scattering (μ_a) and absorption (μ_s)
coefficients at each wavelength on the white and grey
5 matter. The absorption factors are used to determine
oxygen saturation which is then used to detect hypoxia,
localized bleeding and other reversible or irreversible
disorders. The scattering changes in the examined tissue
could be a manifestation of perinventrical hyperintense
10 syndrome (PVH), Alzheimer's disease manifested as plaques
and tangles embedded in the grey matter and others.

As implied in the earlier description, it is
desirable to precisely determine the delay time of the
detected pulse. In systems of Figs 1, 3, and 5, the
15 pulser sends directly a trigger signal to each boxcar
integrator. In the single photon counting TRS-pulse
system, described in the above-cited patent application,
the pulser sends a trigger signal to the time-to-
amplitude converter when a pulse is emitted from the
20 laser. However, when it is desirable to verify the time
delay of the detected pulse, a third, reference fiber of
known length, connected to the PMT detector, is
positioned next to the input port. The detected
reference pulse has a delay proportional to the length of
25 reference fiber, and thus the time delay can be
calibrated.

Fig. 6 shows a block diagram of the dual
wavelength TRS-pulse system adapted to reference the
timing of the input pulse. Laser diodes 122, 124 (e.g.,
30 Hamamatsu PLP 10 laser diode) are driven by a 100 MHz
pulse generator 118 connected to a 5 mW pulser 119. The
light from lasers 122, 124 is time shared electro-

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mechanically by a 60 Hz vibrating mirror 126 so that they
alternately illuminate a fiber coupler 128 that conducts
pulses of light into subject 10. Photons migrate through
the subject 10 to a detection port of a fiber 127 and to
5 the detector 110 that is a photomultiplier.
Additionally, a reference fiber 129 of known length is
located at the input port of fiber 128 and is also
connected to detector 110.

     The output of photomultiplier tube 110 is directly
10 connected to a wide band amplifier 112 with appropriate
roll-off to give good pulse shape and optimal signal to
noise ratio. A high/low level discriminator 113 receives
an output signal from amplifier 112. Discriminator 113
is a pulse amplitude discriminator wherein the threshold
15 for acceptance of a pulse is a constant fraction of the
peak amplitude of the pulse. Next, the discriminator
pulses are sent to a time-to-amplitude convertor (TAC)
114. The time-to-amplitude convertor produces an output
pulse with amplitude proportional to the time difference
20 between start and stop pulses. The pulse – photon
detection cycle is repeated at frequency on the order of
10 MHz to acquire a typical photon distribution. The
multichannel analyzer collects only a single photon for
each input light pulse. Signal from each detected photon
25 is encoded for time delay and recorded. Following the
time to amplitude conversion, the counts corresponding to
the two wavelengths are separately summed in two
multichannel analyzers (MCA) 130, 132, respectively. As
shown in Fig. 6A, each multichannel analyzer collects and
30 stores the time resolved spectrum that consists of
detected pulse (142) modified by the examined tissue and
reference pulse (140) collected by reference fiber 129
(FIG. 6). Since reference fiber 129 is located at the
input port of fiber 128, the delay of the reference pulse
35 is proportional to the known length of reference fiber

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129. By comparing the known delay time of the reference pulse with the detected delay time of the reference pulse (140), the time scale of the scattered pulse (142) can be precisely calibrated.

5   Further embodiments are within the scope of the following claims:

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1. A system for examination of biological tissue
of a subject, the scattering and absorptive properties of
the examined tissue being determined by photons migrating
between an optical input port and an optical detection
5 port of said system, said system comprising:

an optical input port located at a first location
to introduce light to the biological tissue;

an optical detection port located at a second
location spaced apart from said input port to detect
10 light that has migrated through the biological tissue;

a light source coupled to the input port for
introducing into the tissue, at the input port, pulses of
photons of electromagnetic radiation of a selected
wavelength in the visible or infra-red range, said pulses
15 having duration on the order of a nanosecond or less and
having original pulse shapes;

a detector, coupled to the detection port, for
detecting the intensity of pulses of photons, introduced
into the tissue by said light source, that have become
20 modified from their original pulse shapes as a result of
migrating through tissue lying between said input and
detection ports;

a gated integrator, coupled to said detector and
associated with an integrator timing control, for
25 integrating the photons of a detected pulse over at least
two selected time intervals spaced apart over the
duration of said detected pulse; and

a processor, coupled to said integrator, for
determining a physiological property of the examined
30 tissue based on the number of photons integrated over
each of said at least two time intervals.

2. The system of claim 1 further comprising a
second gated integrator, coupled to said detector and
associated with a second integrator timing control, for

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integrating said photons over a selected time interval
spaced over the arrival time of said modified pulses.

3.   The system of claim 1 or 2 wherein said
processor is configured to determine the absorption
5   coefficient (μ_a) of the examined tissue based on the
number of photons integrated over said at least two
selected time intervals.

4.   The system of claim 3, for use under
conditions in which the modified pulses have a decay
10   slope characteristic of a property of tissue through
which said photons have migrated, wherein said processor
is configured to determine the absorption coefficient of
tissue from the decay slope of the detected pulses of
photons.

15   5.   The system of claim 3 wherein said processor
is configured to determine the absorption coefficient by
implementing the formula:

$$\mu_a c = - \frac{d}{dt} \log_e R(\rho, t) + \frac{\rho^2}{4Dct} - \frac{5}{2t}$$

wherein $d[\log_e R(\rho, t)]/dt$ is determined from the
characteristic decay slope of said modified pulses, D is
20   diffusion coefficient for the examined tissue, c is speed
of the light in the tissue, ρ is the distance between
said input and detection ports, and t is the time
relatively close to the time the detected intensity of
the detected modified pulse has a maximum value.

25   6.   The system of claim 3 wherein said gated
integrator, said integrator timing control, and said
processor are configured to determine the delay time
(t_{max}) between the time a pulse is introduced into the

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tissue by said light source and the time the intensity of the corresponding modified pulse, detected by said detector, has a maximum value.

7.   The system of claim 6 wherein said processor is further configured to determine the effective scattering coefficient $(1-g)\cdot\mu_s$ of the examined tissue by implementing the formula:

$$(1-g)\mu_s = \frac{1}{\rho^2}(4\mu_a c^2 t_{max}^2 + 10c t_{max}) - \mu_a$$

wherein ρ is a distance between said input and detection ports and c is speed of the light in the tissue.

8.   The system of claim 1 or 2 further comprising:

a second light source, coupled to said input port, for introducing into the tissue, at said input port, pulses of photons of electromagnetic radiation of a second selected wavelength in the visible or infra-red range, said pulses of photons of the second wavelength having original pulse shapes;

said detector being sensitive to detect, at said detection port, the intensity of pulses of photons at said second wavelength introduced into the tissue by said second light source that have become modified from their original pulse shapes as a result of migrating through tissue lying between said input and detection ports;

said gated integrator and said integrator timing control being capable of integrating said detected photons of the second wavelength over at least two selected time intervals spaced apart over the duration of said detected pulses of photons of the second wavelength; and

said processor being capable of determining a physiological property of the examined tissue based on

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the number of photons integrated over each time interval
for each selected wavelength.

        9.   The system of claim 8 wherein said processor
is configured to determine the absorption coefficient
5 (μ_a), for each selected wavelength, based on the number
of photons of the respective wavelengths integrated over
at least two selected time intervals.

        10.   The system of claim 9 wherein said processor
is configured to determine the concentration of a tissue
10 pigment based on the absorption coefficients determined
for the selected wavelengths.

        11.   The system of claim 9 wherein said processor
is configured to determine the oxygen saturation Y of the
tissue based on the ratio of the absorption coefficients
15 determined for the two selected wavelengths.

        12.   The system of claim 1 or 2 wherein said gated
integrator and said integrator timing control are
constructed and arranged to integrate said detected
photons over several selected time intervals distributed
20 over the entire arrival time of the modified pulses; and
        said processor is configured to determine the
intensity profile, over time, of the detected modified
pulses.

        13.   The system of claim 12 wherein said processor
25 is configured to determine a mean pathlength for the
detected photons that have migrated through the tissue
from said input port to said detection port.

        14.   The system of claim 13 further comprising a
continuous wave oximeter coupled to the output of said

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processor to receive a calibration value representative
of the mean pathlength to enable calibration of data
measured by said oximeter.

15. The system of claim 1 wherein said light
5   source comprises a laser driven by a pulse generator and
a pulser.

16. The system of claim 1 wherein said source of
light is constructed to provide photons having a
wavelength in the range of 600nm to 1000nm.

10   17. A method of examination of biological tissue
of a subject, the scattering and absorptive properties of
the examined tissue being determined by photons migrating
between an optical input port and an optical detection
port, said method comprising the steps of:
15   introducing into the tissue, at the input port,
pulses of electromagnetic radiation of a selected
wavelength in the visible or infra-red range, said pulses
having duration on the order of a nanosecond or less;
        detecting, at the detection port, photons of
20   modified pulses that have migrated in the tissue from the
input port;
        integrating said photons over at least two
selected time intervals separately spaced over the
arrival time of said modified pulses; and
25   determining a physiological property of the
examined tissue based on the number of photons integrated
over each time interval.

18. The method of claim 17 wherein the step of
determining the physiological property comprises the step
30   of determining the absorption coefficient (μ_a) of the
examined tissue as a function of the number of photons

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integrated over at least two selected time intervals
separately spaced over the arrival time of said modified
pulses.

19.   The method of claim 18, for use under
5   conditions in which the modified pulses have a decay
slope characteristic of a property of tissue through
which said photons have migrated, wherein the step of
determining the absorption coefficient comprises
determining said coefficient as a function of the decay
10   slope.

20.   The method of claim 18, for use under
conditions in which the modified pulses have a decay
slope characteristic of a property of tissue through
which said photons have migrated, wherein said step of
15   determining the absorption coefficient comprises
implementing the formula:

$$\mu_a c = - \frac{d}{dt} \log_e R(\rho, t) + \frac{\rho^2}{4Dct} - \frac{5}{2t}$$

wherein $d[\log_e R(\rho, t)]/dt$ is determined from the decay
slope of the arrival time of said modified pulses, D is
diffusion coefficient for the examined tissue, c is speed
20   of the light in the tissue, ρ is the distance between
said input and detection ports, and t is the time
relatively close to the time the intensity of the
detected modified pulses has a maximum value.

21.   The method of claim 18 further comprising the
25   step of determining a delay time (t_{max}) between the time a
pulse is introduced into the tissue and the time the
intensity of the detected corresponding modified pulse
has a maximum value.

22.   The method of claim 21 further comprising the
step of determining the effective scattering coefficient
$(1-g) \cdot \mu_s$ of the examined tissue using the formula:

$$(1-g) \mu_s = \frac{1}{\rho^2} (4\mu_a c^2 t_{max}^2 + 10 c t_{max}) - \mu_a$$

wherein ρ is a distance between said input and detection
5 ports and c is speed of light in the tissue.

23.   The method of claim 17 further comprising the
steps of:
        introducing into the tissue, at said input port,
said pulses of electromagnetic radiation of a second
10 selected wavelength in the visible or infra-red range;
        detecting, at said detection port, photons of
modified pulses of said second wavelength that have
migrated in the tissue from said input port;
        integrating said detected photons over at least
15 two selected time intervals separately spaced over the
arrival time of said modified pulses; and
        determining a physiological property of the
examined tissue based on the number of photons integrated
over each time interval for each selected wavelength.

20   24.   The method of claim 23 wherein said
physiological property is absorption coefficient (μ_a) at
each selected wavelength and said step of determining is
performed by said processor based on the number of
photons integrated over at least two selected time
25 intervals separately spaced over the arrival time of said
modified pulse.

25.   The method of claim 24 further comprising the
step of determining concentration of a tissue pigment
based on said absorption coefficients at each selected
30 wavelength.

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26. The method of claim 24 further comprising the step of determining the oxygen saturation Y based on the ratio of said absorption coefficients at each selected wavelengths.

5   27. The method of claim 17 wherein said integrating step is performed to collect detected photons over several selected time intervals separately spaced over the entire arrival time of said modified pulses; and further comprising the step of

10   determining intensity profile of said modified pulses over the entire arrival time.

28. The method of claim 27 further comprising the step of determining a mean pathlength of the distribution of the photon migration pathlengths.

15   29. The method of claim 28 further comprising the step of calibrating data measured by a continuous wave oximeter using said mean pathlength.

30. The method of claim 17 wherein said step of introducing pulses, comprises introducing pulses of a

20 selected wavelength in the range of 600nm to 1000nm.

31. The system of claim 1 wherein said light source is constructed and arranged to provide light pulses in the infrared range.

32. The method of claim 17 wherein the step of

25 introducing pulses, comprises introducing pulses of a selected wavelength in the near infrared range.

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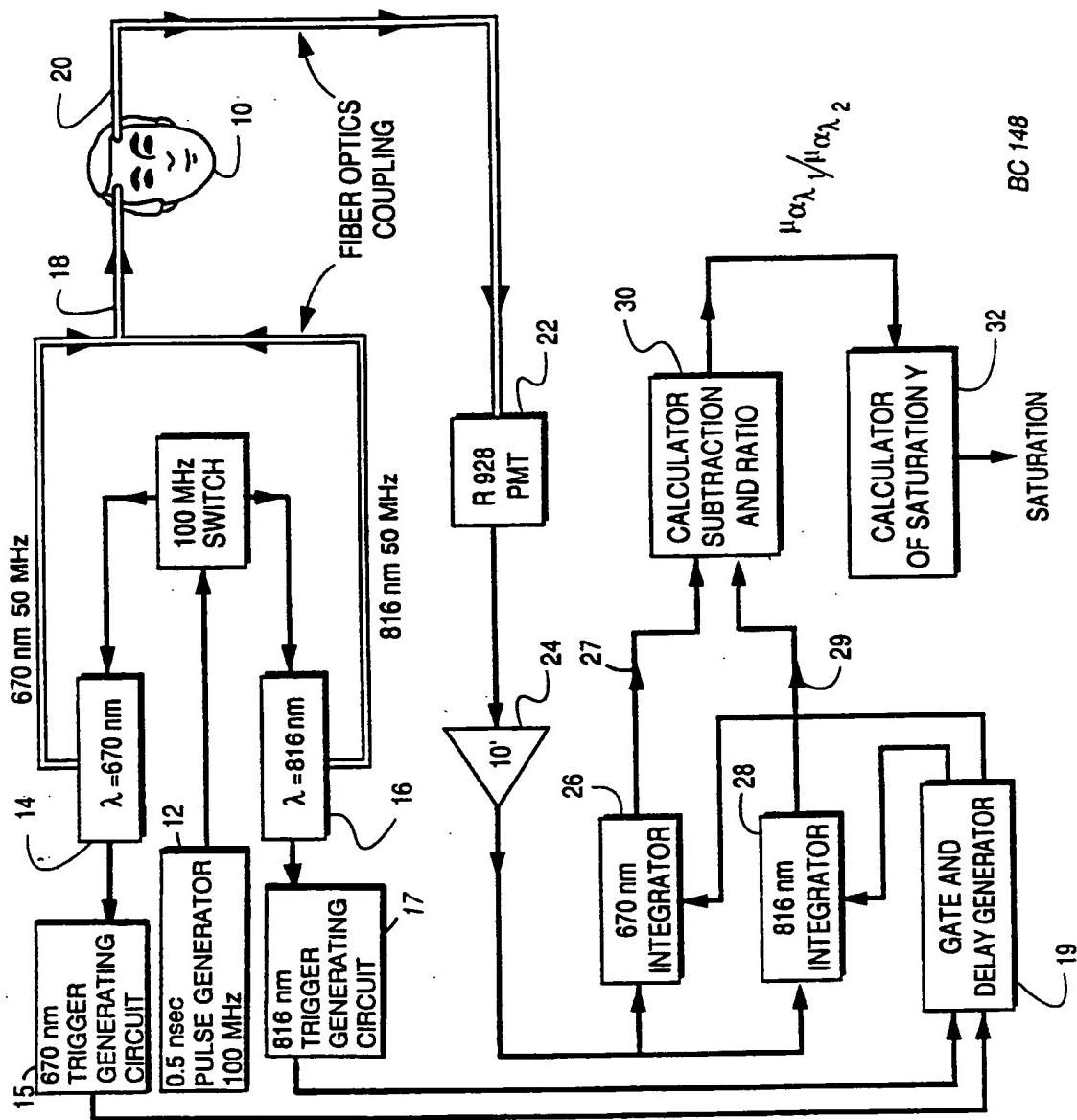
FIG. 1

FIG. 2

TIMING DIAGRAM
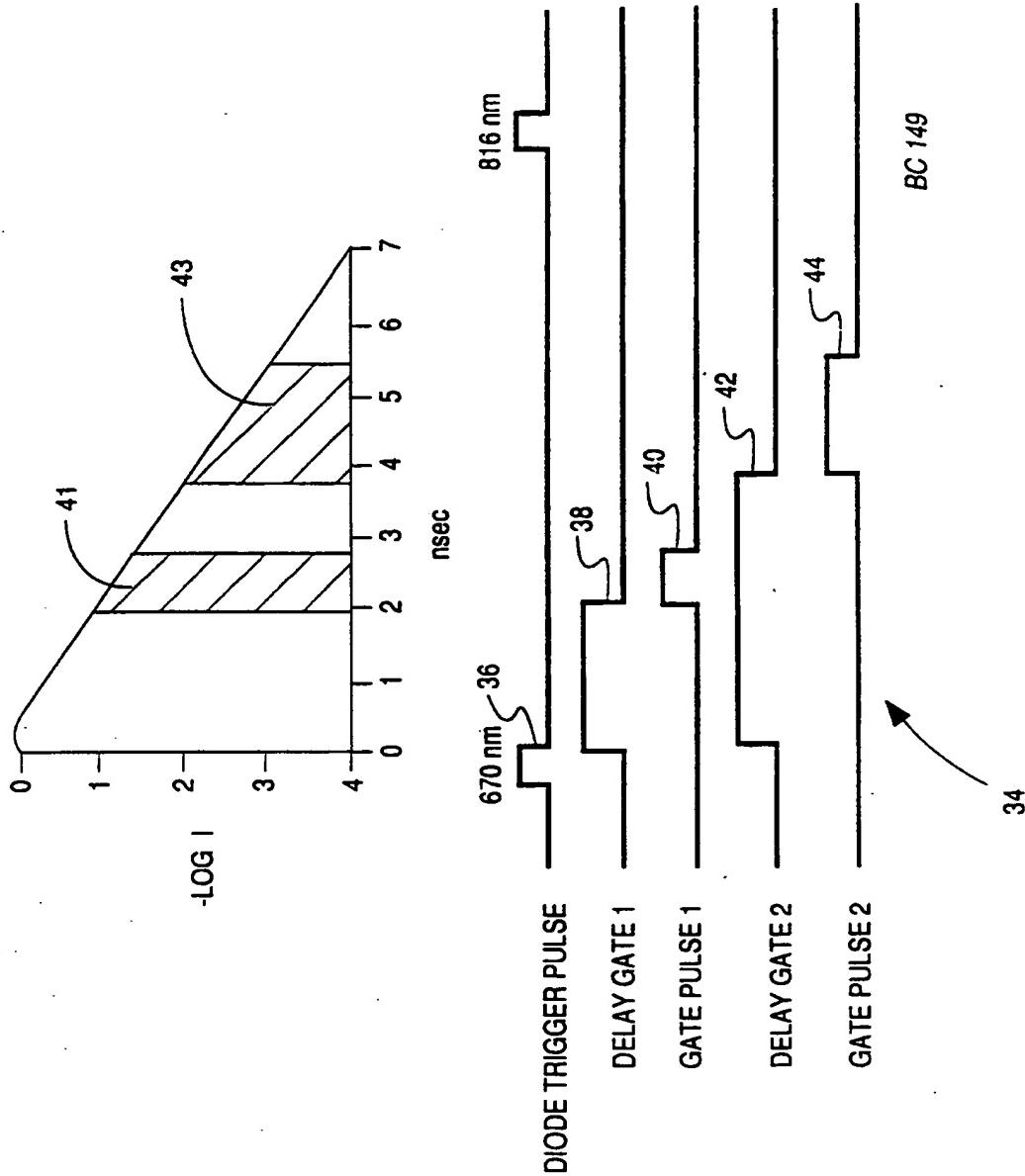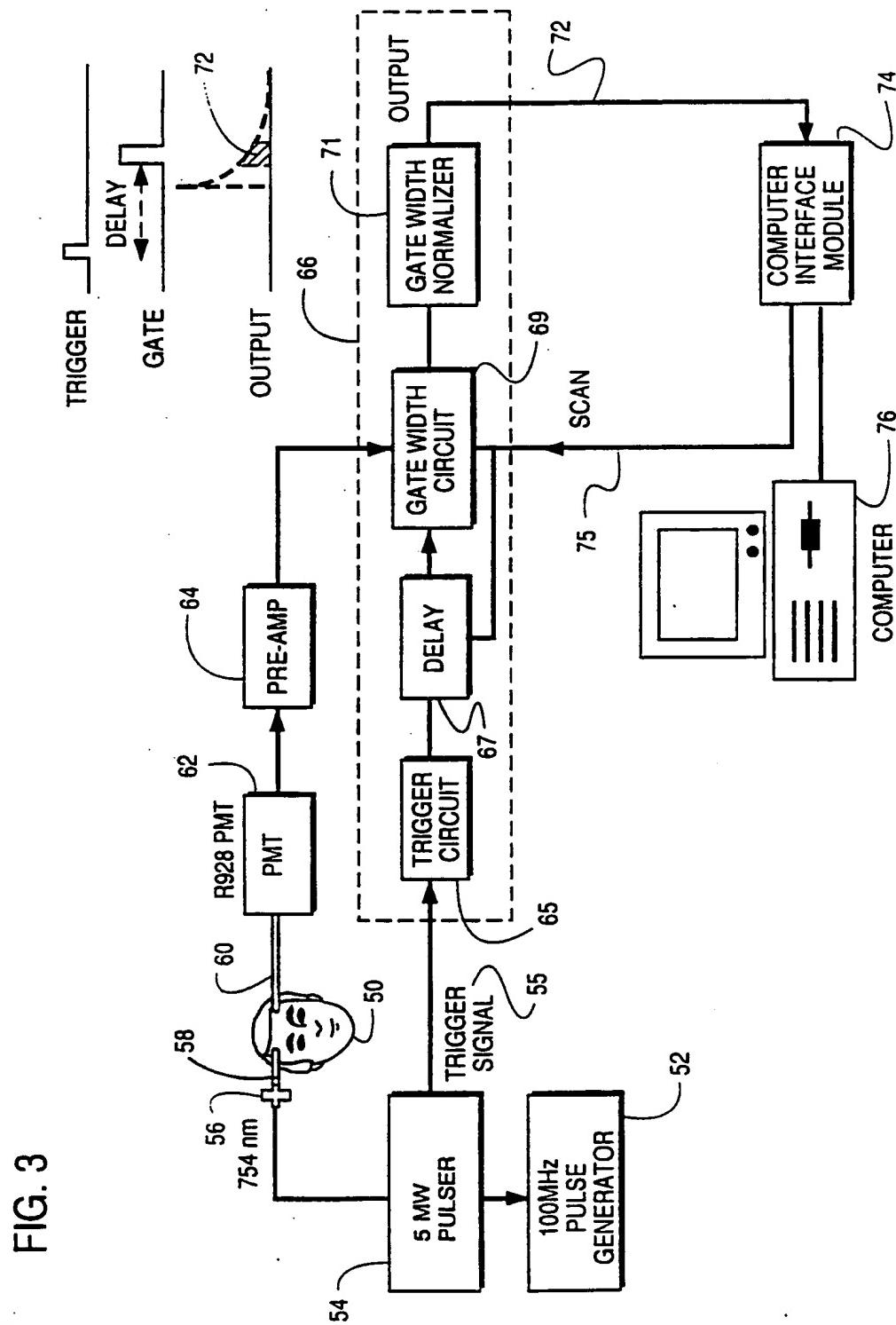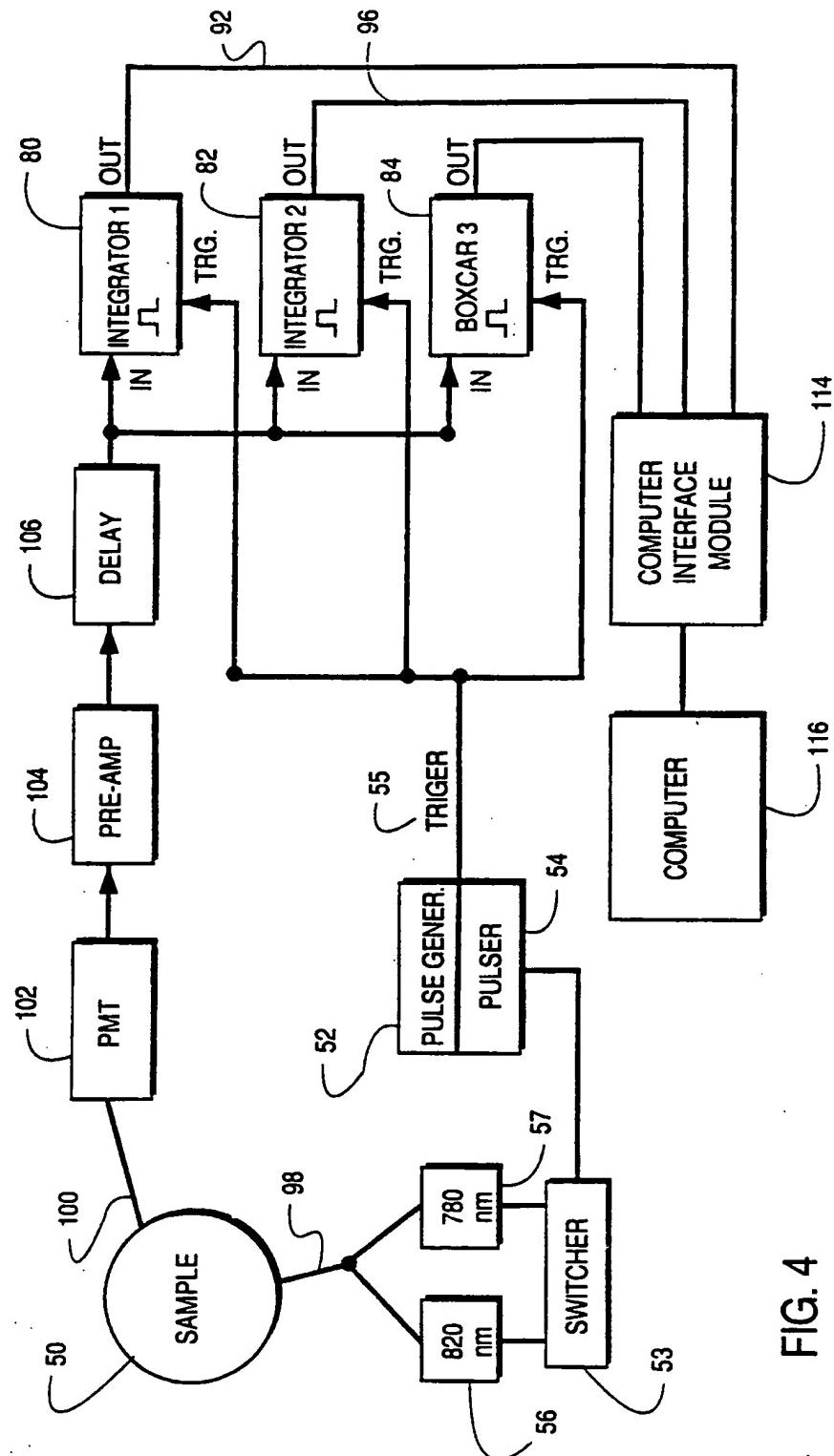
-LOG I

nsec

43

41

DIODE TRIGGER PULSE   670 nm   36

DELAY GATE 1   38

GATE PULSE 1   40

DELAY GATE 2   42

GATE PULSE 2   44

816 nm

BC 149

34

FIG. 3

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FIG. 4

FIG. 5

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FIG. 5A

FIG. 5B

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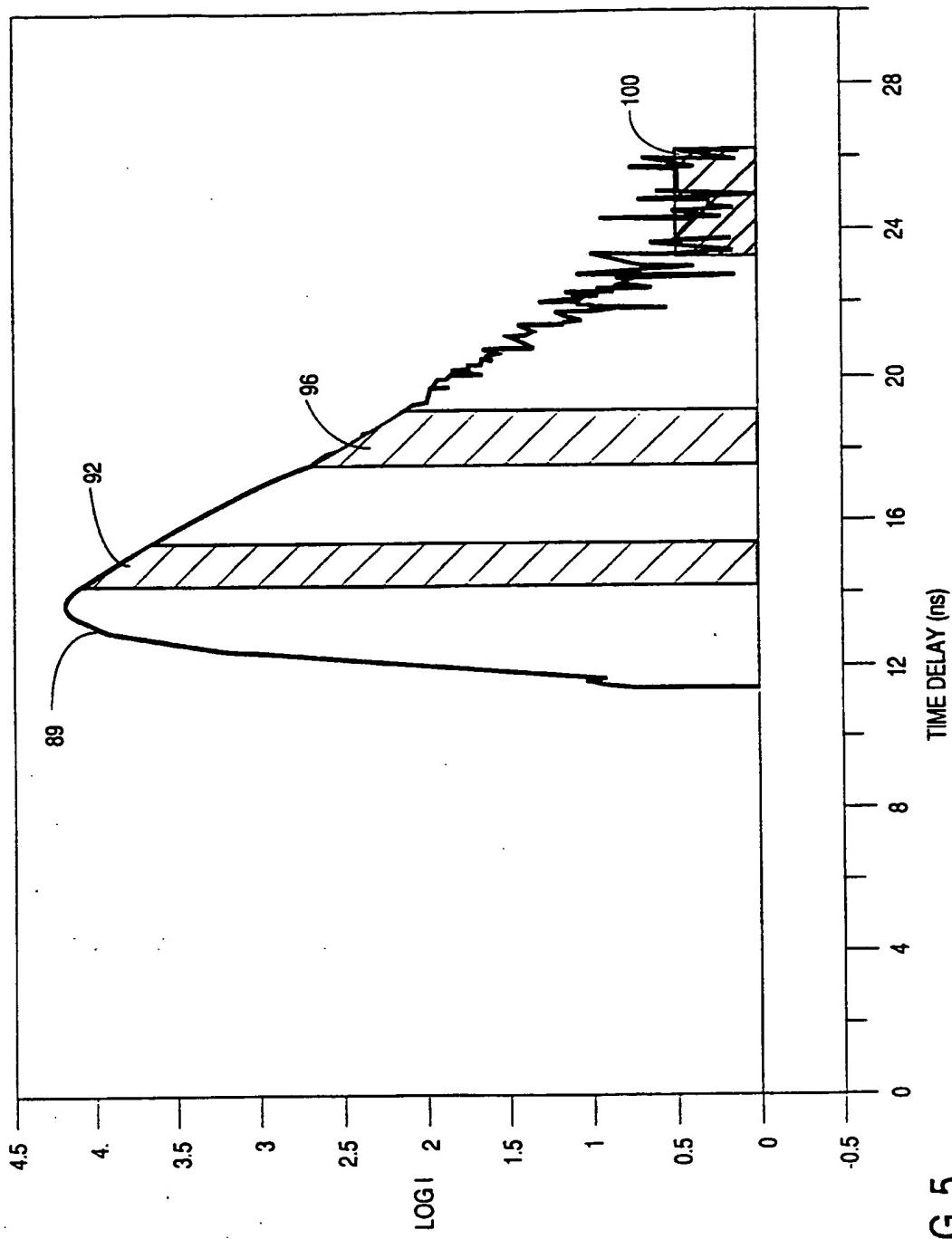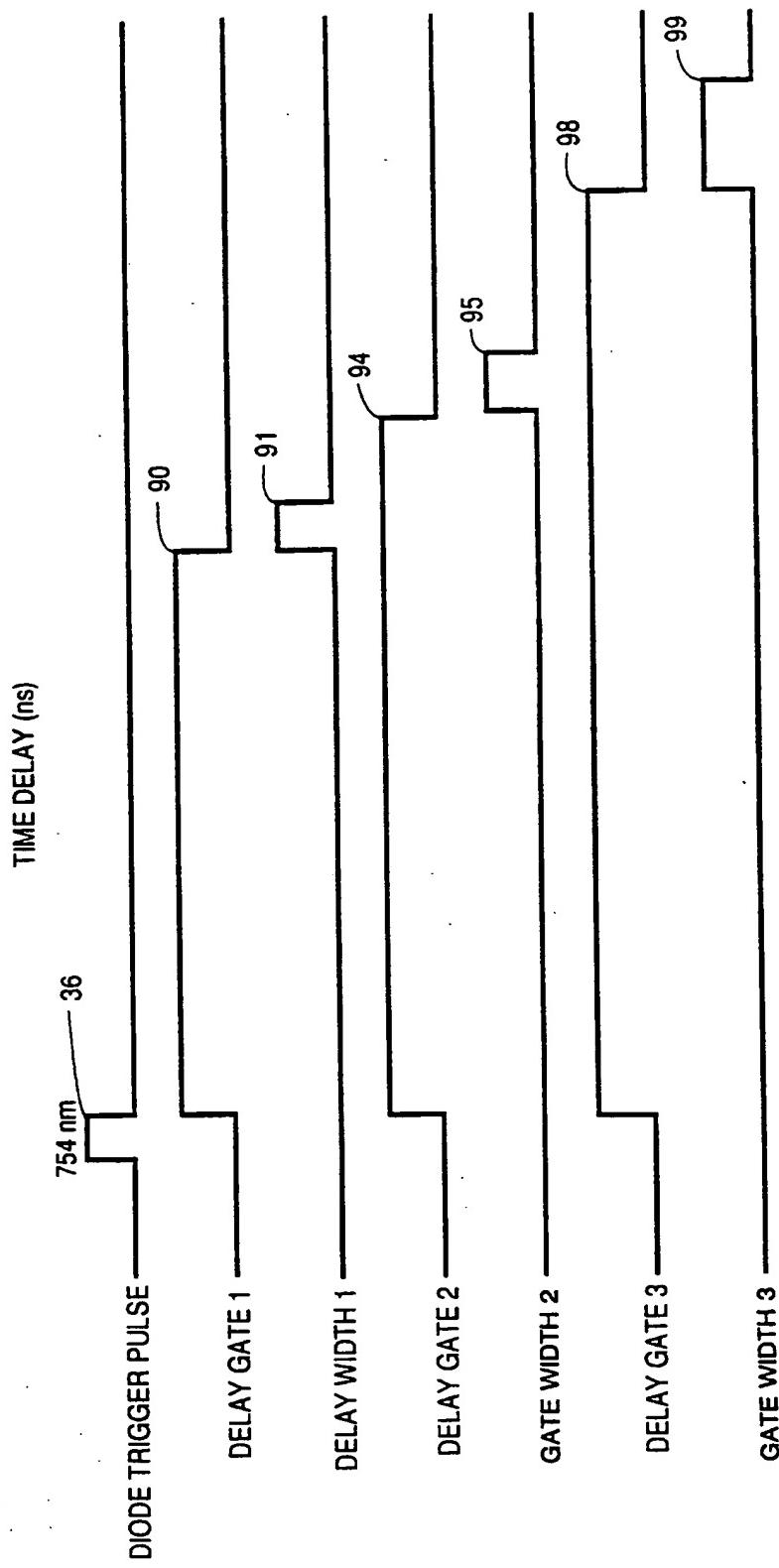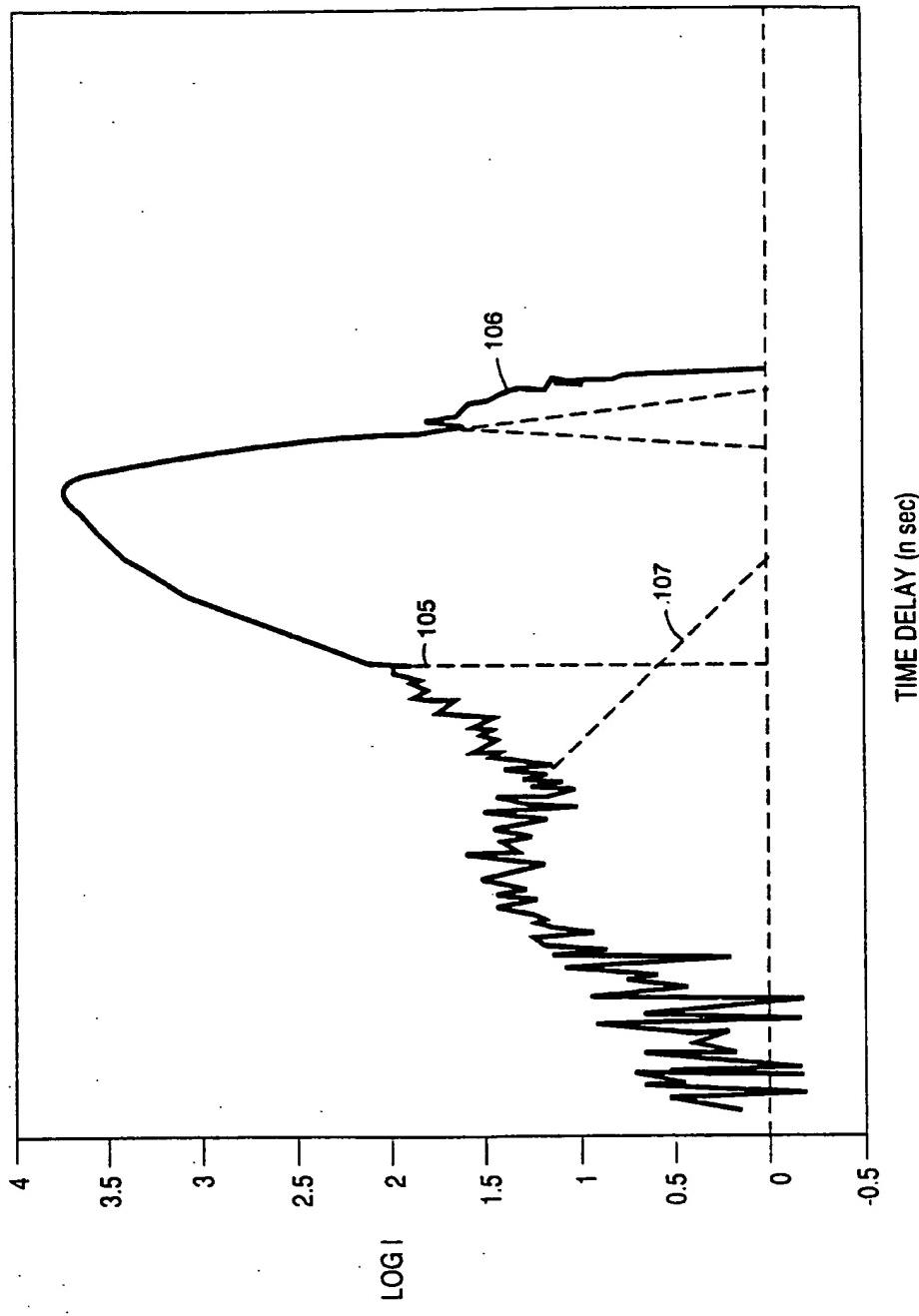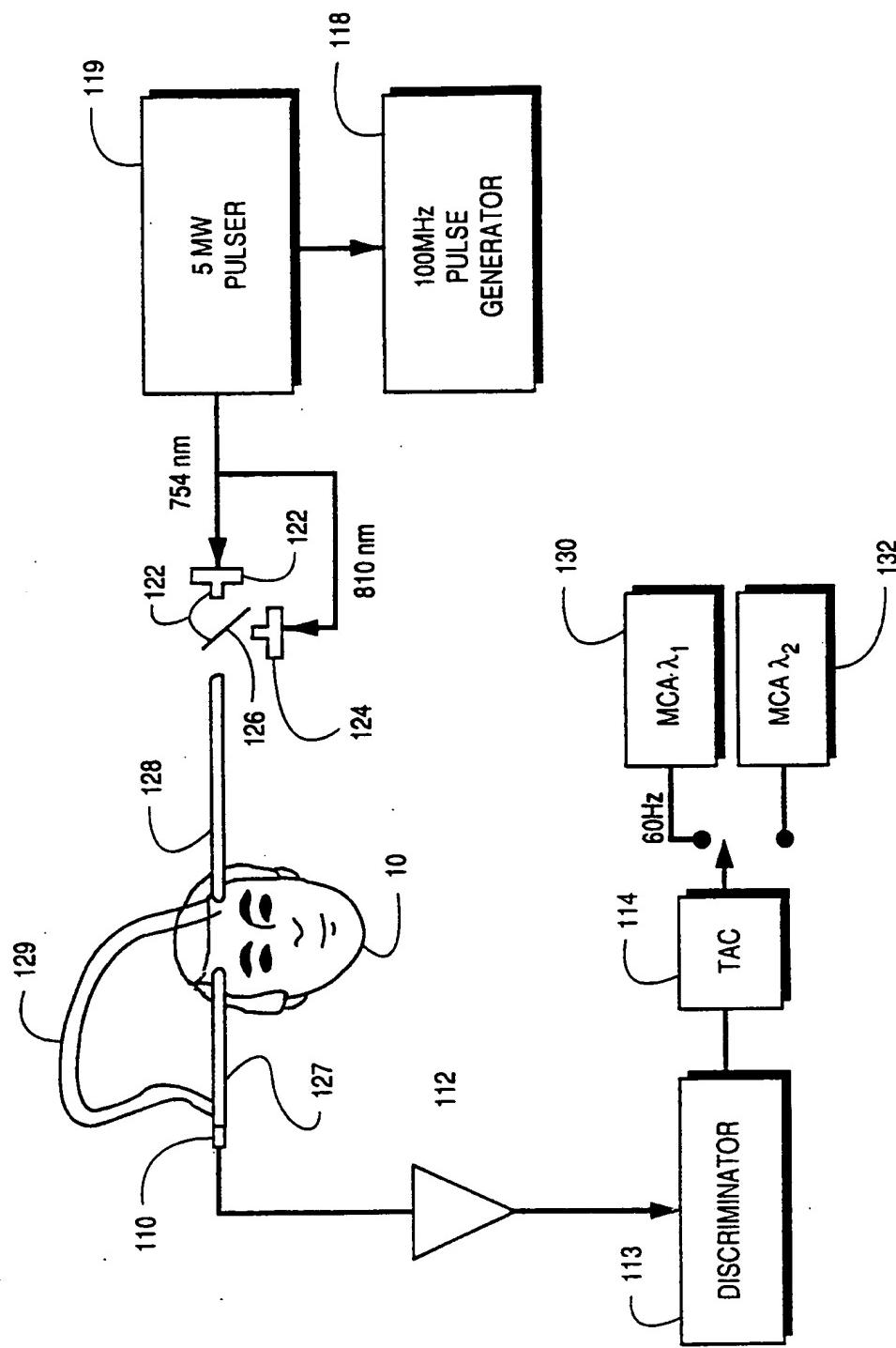
FIG. 6

FIG. 6A
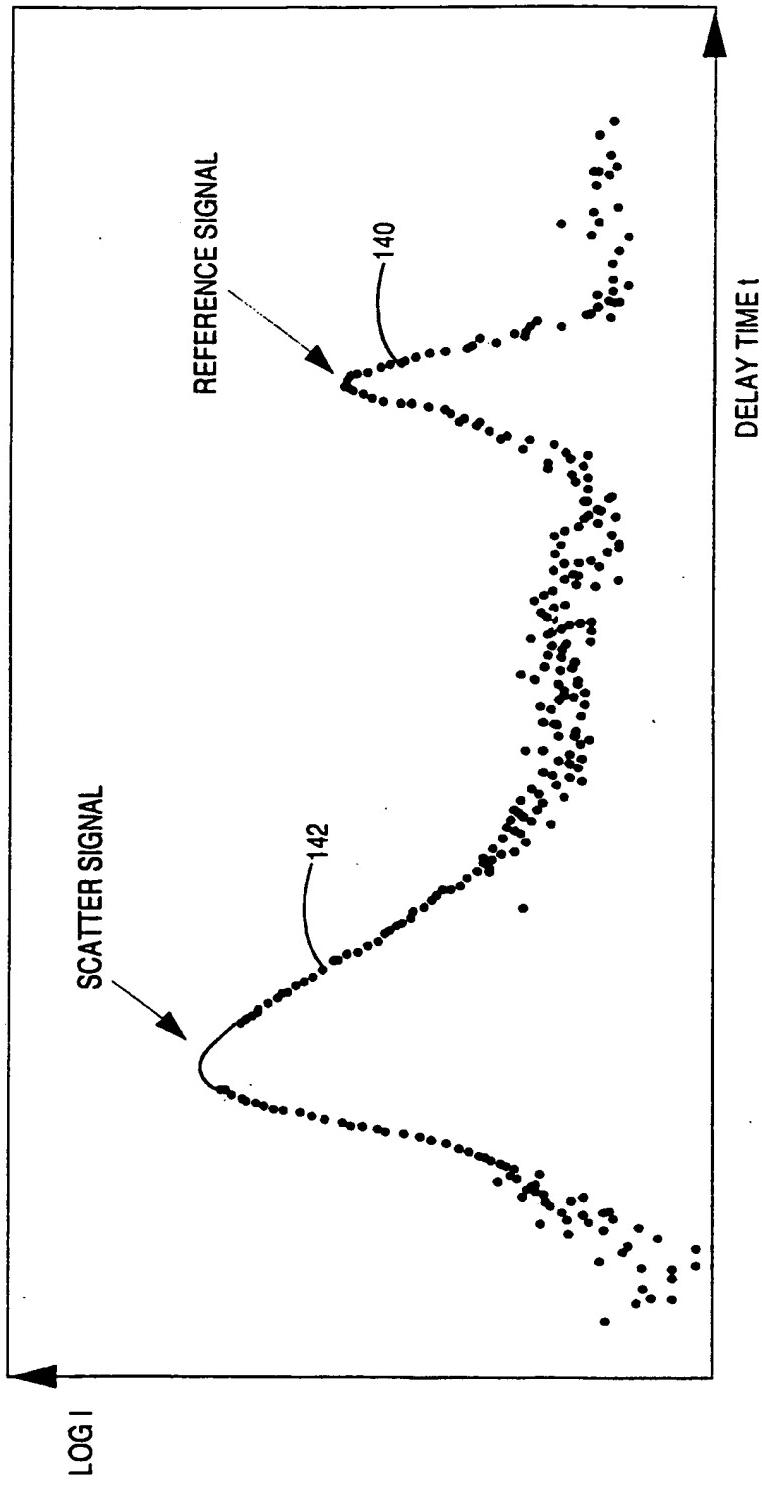
A.	CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61B 5/00
US CL :128/633, 664, 665

According to International Patent Classification (IPC) or to both national classification and IPC

B.	FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/633, 664, 665; 356/39-41; 250/339,341

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

None

C.	DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 4,895,156, (SCHULZE), 23 January 1990. See entire document.	1, 3-7, 9-13, 15, 16 -------------- 31

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:
"A"	document defining the general state of the art which is not considered to be part of particular relevance
"E"	earlier document published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed

"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 APRIL 1994	JUN 07 1994

Name and mailing address of the ISA/US	Authorized officer
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